Troglitazone monotherapy

	FPG, mg/dl		GDR	
	Baseline	3 months	baseline	3 months
Non-responders				
[redacted]	268	247	16	71
	133	139	358	309
	168	159	315	454
	339	336	213	211
	211	266	130	184
	289	263	270	319
	171	172	195	142
Responders				
[redacted]	288	200	88	211
	369	278	116	380
	281	144	148	235
	352	143	117	347
	339	263	123	220
	268	211	142	359

* approximation due to missing data

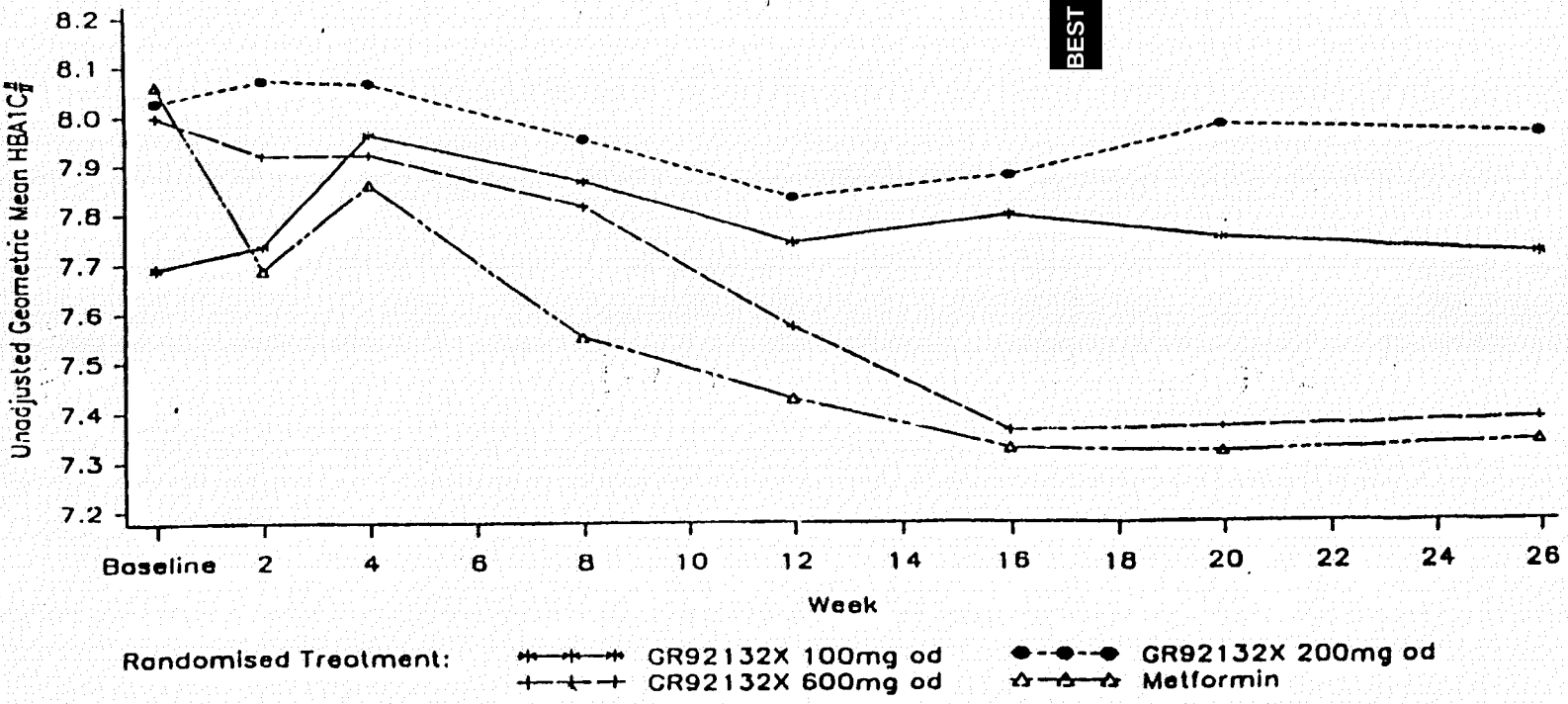
I conclude from this study that troglitazone monotherapy reduces plasma glucose levels by increasing glucose disposal. However, troglitazone monotherapy was not effective in a majority of patients. Metformin's primary action appears to be to decrease hepatic glucose production. That the two agents are more effective when used together than when used alone seems likely, but failure to continue some patients on monotherapy during the second part of the study makes it impossible to exclude the possibility that improvement in hyperglycemia attributed to combination therapy was really just a delayed manifestation of monotherapy.

[redacted] Study 3002

Comparison of troglitazone 100, 200, 600 monotherapy with metformin monotherapy

This was a double dummy-blinded comparison of 3 doses of troglitazone with a metformin titration.. Patients were started on 500 mg bid of metformin and were titrated to a maximum of 3g "at the discretion of the investigator", which I presume to be based on tolerability and efficacy. If patients had been on previous antidiabetic medication, this was discontinued 4 weeks before randomization. One patient had been on a biguanide, the rest had been on a sulfonylurea (58-64% or glucosidase inhibitor (4-12%). There was a small baseline imbalance in that 78% of the patients randomized to metformin had been on previous therapy compared to 65-70% in the troglitazone groups. Patients were randomized if the FSG was between 7-and 15 mM (135 – 270 mg/dl) on two occasions off previous medication. The primary measure of efficacy was change in HbA1c after 26 weeks. As shown in the figure, 600 mg of troglitazone was approximately equivalent to metformin based on HbA1c changes at 16-26 weeks, but lower doses of troglitazone were inferior.

FIGURE 2. HBA1C (%) AGAINST TIME: INTENT-TO-TREAT POPULATION



# Where a measurement has not been recorded, the last non-missing, post baseline assessment is carried forward.
HBA1C = Glycosylated haemoglobin.
Source data: Table 18.

Changes in HbA1c, FSG and fructosamine at endpoint are shown in the table. 600 mg troglitazone was equivalent to metformin based on Hb A1c and FSG, but metformin was better based on fructosamine. Lower doses of troglitazone were inferior by all measures of glycemic control. However, troglitazone was better than metformin at reducing insulin levels Fasting insulin levels were 23% lower with 600 mg troglitazone ($p< 0.001$), 20% lower with 200 mg troglitazone ($p<0.001$) and 15% lower with 100 mg troglitazone ($p<0.02$) than metformin. However, weight reduction was greater with metformin than troglitazone. Also, changes in lipid parameters favored metformin which had lower levels of total cholesterol, LDL cholesterol, VLDL cholesterol and a higher total cholesterol/HDL cholesterol ratio.

Table 6

Glycaemic Parameters at week 26 Table 6

	GR92132X 100mg od	GR92132X 200mg od	GR92132X 600mg od	Metformin 1000-3000mg od
HbA_{1c} (%)				
n @	93	91	96	92
Week 26 value*	7.9	7.9	7.3	7.3
% change from metformin	8	8	1	-
p-value #	0.002	0.002	0.737	-
Fasting serum glucose (mmol/L)				
n @	93	91	98	95
Week 26 value*	10.3	10.0	9.2	9.0
% change from metformin	11	11	2	-
p-value #	<0.001	0.002	0.489	-
Fructosamine (µmol/L)				
n @	93	91	98	95
Week 26 value*	360	353	343	312
% change from metformin	16	13	10	-
p-value #	<0.001	<0.001	<0.001	-
Fructosamine corrected for total protein (µmol/g)				
n @	91	90	96	94
Week 26 value*	5.0	5.0	4.8	4.3
% change from metformin	16	15	12	-
p-value #	<0.001	<0.001	<0.001	-

* adjusted geometric mean (adjusted for geographical region and baseline)

p-value from analysis of covariance of log transformed data - compared to metformin

@ number of patients in the ITT Population with a value at baseline and week 26. Where a week 26 value was not recorded, the last non-missing post-baseline value was carried forward.

Table 7

than on metformin for the GR92132X [illegible]

Lipid Parameters at week 26 Table 7

	GR92132X 100mg od	GR92132X 200mg od	GR92132X 600mg od	Metformin 1000-3000mg od
Total cholesterol (mmol/L)				
n @	93	91	98	95
Week 26 value*	5.9	5.9	6.3	5.6
% change from metformin	5	6	13	-
p-value #	0.029	0.012	<0.001	-
HDL-cholesterol (mmol/L)				
n @	92	89	98	94
Week 26 value*	1.0	1.0	1.0	1.0
% change from metformin	-3	-1	4	-
p-value #	0.298	0.761	0.162	-
Triglycerides (mmol/L)				
n @	93	91	98	95
Week 26 value*	1.84	1.77	1.69	1.81
% change from metformin	2	-2	-7	-
p-value #	0.764	0.712	0.197	-
NEFA (µmol/L)				
n @	93	91	98	95
Week 26 value*	474	462	445	524
% change from metformin	-9	-12	-15	-
p-value #	0.160	0.077	0.020	-
LDL-cholesterol (mmol/L)				
n @	92	89	98	94
Week 26 value*	4.5	4.6	4.9	4.3
% change from metformin	5	6	13	-
p-value #	0.144	0.059	<0.001	-
VLDL-cholesterol (mmol/L)				
n @	85	87	93	90
Week 26 value**	0.2	0.2	0.3	0.2
p-value ##	0.030	0.010	<0.001	-
Total cholesterol:HDL-cholesterol ratio				
n @	92	89	98	94
Week 26 value*	6.02	5.93	5.99	5.55
% change from metformin	9	7	8	-
p-value #	0.036	0.090	0.047	-

* adjusted geometric mean (adjusted for geographical region and baseline) **median value
# p-value from analysis of covariance of log transformed data - comparison to metformin
p-value from van Elteren extension to Wilcoxon rank sum test - comparison to metformin
@ number of patients in the ITT Population with a value at baseline and week 26. Where a week 26 value was not recorded, the last non-missing post-baseline value was carried forward.

The average final dose of metformin was 1.55 g. Although the maximal labeled dose is 2.55g (850 mg tid), the most commonly used metformin dose was 2g (1g bid). Similar final doses of metformin placebo were taken by patients in the troglitazone groups. The results of this study show that 600 mg of troglitazone (maximum approved dose) is roughly equivalent to 1.5g of metformin (submax dose) with respect to HbA1c and fasting glucose, but not quite equivalent with respect to fructosamine. Metformin was better with respect to body weight and lipids. It is not clear why fructosamine gives a different result from HbA1c and fasting serum glucose.

Although the study claims to have shown equivalence between 600 mg of troglitazone and a titrated dose of metformin, FDA's statistical reviewer, Lee Pian, has raised doubts about this claim on methological grounds. It should also be noted that the claim of equivalence is based entirely on mean data. The Sponsor never submitted individual data nor submitted a responder analysis. Given the large variability in individual responses to troglitazone monotherapy, I think that the claim of equivalence to metformin is not well established.

Protocol 2019
Effect of troglitazone body composition

This was a [redacted] study designed to determine if troglitazone changes the distribution of body fat in patients with type 2 diabetes. Previous studies have shown that effective glucose lowering treatment with troglitazone is associated with an increase in body weight. This is generally considered to be undesirable given that most patients with type 2 diabetes are obese and that obesity itself contributes to insulin resistance and hyperglycemia. However, troglitazone may also promote fluid retention and some of the increase in body weight in troglitazone- treated patients may be due to fluid and not fat. Also, it is generally recognized that intraabdominal fat is a more important risk factor for cardiovascular disease than increased body fat alone. This study was apparently done in the hope of dispelling the fear that increased body weight in patients on troglitazone may be harmful.

This was a 12-week study comparing 600 mg of troglitazone to placebo. Patients were allowed to continue sulfonylureas provided that there had not been a change in dose for the previous three months. In addition to glucose, HbA1c, insulin and lipid levels, total body fat was measured by anthropometric measurements, by underwater weighing and intrabdominal fat was determined by MRI. The placebo group consisted of 8 men and 3 women. The troglitazone group consisted of 8 men and 4 women. There mean age was 58 years and there mean weight was 80 kg.

Results are shown below:

	Troglitazone, n=12		Placebo, n=12	
Total body fat,%	Anthropometric	underwater	Anthropometric	underwater
Day 0	37.00	34.46	36.08	35.48
Day 84	36.95	33.88	34.92	32.89
Intra-abdominal fat, L				
Day 0	3.20		3.27	
Day 84	2.62		3.18	
Delta	-0.58		-0.08 (n=11)	
Total abdominal fat, L				
Day 0	6.31		5.97	
Day 84	5.64		5.67	
Delta	-0.67		-0.21 (n=11)	

There was a trend toward reduction in intraabdominal fat in the troglitazone-treated patients, but none of the changes were statistcally significant, neither change from baseline nor differences between troglitazone and placebo.

Changes in glycemic indices and lipids are shown in the following table.

Table 5

Protocol No. THZB2019

TABLE 4. SUMMARY STATISTICS FOR FASTING DATA

	GR92132X 600mg				Placebo			
	N	Mean (sd)	N*	Chg (sd)	N	Mean (sd)	N*	Chg (sd)
Fasting glucose (MMOL/L)								
Screening	12	10.68 (2.69)			10	12.02 (2.87)		
Day 84	12	9.83 (3.32)	12	-0.85 (3.80)	10	11.76 (2.32)	9	0.08 (2.83)
Fasting HbAlc (%)								
Screening	12	7.79 (1.64)			10	8.45 (1.48)		
Day 84	12	6.54 (1.03)	12	-1.25 (1.05)	8	8.65 (1.36)	7	0.31 (1.04)
Fasting insulin (MU/L)								
Screening	12	16.31 (9.16)			10	17.43 (8.30)		
Day 84	12	12.18 (7.16)	12	-4.13 (6.73)	10	13.72 (6.72)	9	-4.01 (4.14)
Fasting triglyceride (MMOL/L)								
Screening	12	2.61 (1.60)			11	8.39 (14.61)		
Day 84	12	2.91 (2.40)	12	0.30 (1.10)	10	3.25 (3.10)	10	-1.00 (2.26)
Fasting total cholesterol (MMOL/L)								
Screening	12	5.97 (1.19)			11	7.69 (4.36)		
Day 84	12	6.01 (1.16)	12	0.04 (0.76)	10	6.22 (1.15)	10	-0.19 (0.80)
Fasting LDL-cholesterol (MMOL/L)								
Screening	0	.			0	.		
Day 84	1	3.70	0	. (.)	0	.	0	. (.)
Fasting HDL-cholesterol (MMOL/L)								
Screening	9	1.06 (0.18)			8	1.06 (0.19)		
Day 84	9	1.02 (0.25)	9	-0.04 (0.14)	8	1.08 (0.19)	7	-0.01 (0.06)
Fasting leptin (NG/ML)								
Screening	12	10.95 (8.41)			11	11.92 (9.83)		
Day 84	12	13.36 (9.34)	12	2.41 (2.54)	10	11.40 (9.16)	10	1.19 (3.04)

* = Subjects who have both data at screening and at Day 84
Chg = Change from screening visit

The following points are of particular interest:

Measures of glucose control changed little in the placebo group. In the troglitazone group, mean HbA1c levels fell 1.25%units but fasting glucose levels fell only 0.85 mM. A fall of 1.25% units in HbA1c should ordinarily be associated with a fall in fasting serum glucose of about 2.5mM. The wide discrepancy between these two measures of glucose control can best be explained by a change in glycemic control that occurred PRIOR to initiation of troglitazone treatment. Patients were required to be on a stable dose of SFU for three months. But three months is not adequate time to see a full effect of troglitazone on HbA1c. Thus, part of the fall in HbA1c observed during troglitazone may have been a carry-over from a previous change in SFU dose.

In previous studies, Parke Davis has used a reduction of FSG of 1.67mM (30/mg/dl) at 6 weeks as a criteria for an adequate response. Based on a mean reduction in serum glucose of only 0.85mM (15 mg.dl) after 12 weeks, the average response of the patients in this study would have to be classified as inadequate. The lack of change in body fat distribution is therefore of little interest. Since there were only 12 patients in the troglitazone group, I examined the individual data of patients who had a change of over 4 mM (7.2 mg/dl) glucose in either direction. Of the three patients who had a reduction in FSG > 4mM, all three had a rise in body weight and increase in % fat by the anthropometric measurement. In the two patients whose FSG rose by over 4 mM, there was little change in body weight but a fall in % fat by anthropometric measure. Changes in % body fat by underwater weighing did not appear to correlate with changes in glucose. Given the small number of patients and apparent inconsistency of results, I think that any general claim regarding changes in body fat during troglitazone therapy should be rejected.

CHANGES IN MEASUREMENTS AFTER 81 DAYS

Pt number	FSG, mM	HbA1c	Weight, kg	anthropometric % fat	underwater %fat
9033	-5.1	+0.4	+2.4	+2.0	-0.2
9034	-4.9	-1.4	+2.2	+4.3	-2.0
9044	-4.9	-1.7	+19.1	+3.3	+0.5
9042	+5.0	-3.3	0.0	-7.1	-1.6
9048	+7.3	-0.8	+2.2	-1.5	+4.3

It is also worthy of note that mean fasting triglycerides rose slightly in the troglitazone group but fell in the placebo group. The mean fall in the placebo group is probably due to an outlier with a very high initial value. However, the rise in triglyceride is atypical of troglitazone treatment. In summary, this is a very small study and the results are inconsistent. Any conclusions from this study are highly suspect and should not be included in labeling.

REVIEW OF HEPATOTOXICITY

Mean transaminase levels fell in patients treated with troglitazone in phase 3 trials, probably reflecting improvement in steatosis that is frequently present in livers of patients with poorly controlled diabetes. One patient had a baseline ALT elevation of 148 U/l which normalized to 18 U/l on troglitazone. A second patient had a baseline elevation of 98 which fell to 53 on troglitazone.

The initial labeling for troglitazone contained information about two patients* who developed reversible jaundice during the trials and had biopsy findings of "idiosyncratic drug reaction." It was also stated that 2.2% of patients during the trials had a transaminase (ALT or AST) level exceeding 3xULN. In many of these patients, ALT levels fell despite continuation of troglitazone treatment. With only two cases of jaundice in a database of over 2500 patients, it was not apparent that routine liver monitoring would have been productive. As noted above, ALT elevation due to diabetes itself appeared to be improved by troglitiazone. Since the treatment-emergent elevation was reversible in all cases, inclusion of the data mentioned above in the warnings and laboratory abnormalities sections was thought to have been adequate.

What was not appreciated by DMEDP was that many of the patients classified as ALT > 3xULN actually had ALT values that were VERY much greater than 3xULN.

The first cases of frank liver failure related to troglitazone surfaced in October 1997, and required a reassessment of the data from the clinical trials. On October 21, 1997, Parke Davis submitted a document to their IND (IND [redacted] summarizing the experience regarding abnormal liver tests from the clinical trials based on information available through February 1, 1997. These data are summarized in the table below. Of patients with treatment emergent ALT values >3x ULN, the median study duration to peak ALT elevation was 121 days. There were 24 patients in whom troglitazone was discontinued because of an ALT elevation. In reviewing these data, I believe that one of these cases could be explained by preexisting elevation . 22 of the remaining 23 patients had treatment-emergent ALT values over 3x ULN. The highest baseline value was 65 U/L (1.9 x ULN) In 14 of these 23 patients, the ALT value exceeded 8xULN (272 U/L based on normal ALT up to 34 U/L) and in 5/23 patients the ALT value exceeded 30xULN.. There were also 17 patients who developed ALT elevation > 3x ULN while on troglitazone in whom the abnormality reversed despite continuation of troglitazone. In 5 of these patients, ALT exceeded 8xULN. The highest value was 12 xULN. There were additionally 8 patients with ALT > 3xULN with elevations that persisted at the end of the trial but whose ALT normalized following completion of troglitazone treatment. ALT elevations appeared to occur more frequently in the Glyburide add-on trial than in the other trials. Among 237 patients treated with troglitazone plus glyburide, six patients were withdrawn because of ALT elevations and five patients had ALT elevation that normalized despite continued treatment. Among 236 patients on troglitazone alone, one was withdrawn because an ALT elevation, three normalized despite continued treatment, and two normalized after troglitazone was withdrawn. The total number of patients was 11 /237 (4.6%) for glyburide plus troglitazone and 6/236(2.5%) for troglitazone alone. Before concluding that glyburide may increase the risk of hepatic toxicity due to troglitazone, one must assess possible differences in the length of exposure. This trial was a 12 month comparison of troglitazone plus glyburide to troglitazone alone. Although equal numbers of patients were randomized to troglitazone plus glyburide (n=237) as troglitazone alone (n= 236), the dropout rate due to lack of efficacy was very high for patients on troglitazone alone. 90 patients on troglitazone alone completed the study compared to 180 patients on troglitazone plus glyburide. The troglitazone vs placebo trials only lasted six months, and were also associated with a high drop-out rate because of lack of efficacy. Thus, part of the apparent increase in troglitazone hepatotoxicty in patients on glyburide may be due to longer exposure. On the other hand, it should be noted that only 3 of the 11 patients on glyburide plus troglitazone and 1 of the 6 patients on troglitazone alone had their ALT elevation after 180 days.

Some of the data, which Parke Davis submitted on October 21, 1997, appeared inconsistent with the section on "abnormal liver function tests" in the text of the safety update of May 21, 1997 which Parke-Davis submitted prior to approval of the efficacy supplements for monotherapy and the combination of troglitazone with sulfonylureas. In response to a request for clarification, Parke Davis explained that two patients mistakenly described in the safety update as having ALT values <3xULN actually had values >3xULN. One of these had an ALT of 1111. In addition, PD explained that the discussion of patients with elevated ALT levels in the text of the safety update pertained to patients reported as "elevated ALT levels" as the COSTART term. Patients were apparently not included in this section if the COSTART term was "liver function test abnormal".

NDA Data base
ALT Elevations during Clinical Trials

ALT max	Continued on drug Value at end of trial		Withdrawn	Total
	Normal	Abnormal**		
>3 xULN (102 U.L)	17	8	23	48 (1.9%)
>5xULN (140 U/L)	16	6	20	42 (1.7%)
>8xULN (272 U/L)	5	3	14	22 (0.9%)
>30xULN (1020U/L)	---	---	5*	5* (0.2%)

Data from submission to IND [redacted] October 21, 1997
Upper limit of normal taken as 34U/L
N= 2510 (n= 1715, 3 months of longer)

* 2 jaundiced
** normalized following drug withdrawal

It is worthy of note that the incidence of abnormal ALT values in the NIH diabetes prevention trial terminated in June 1998 appears somewhat higher than that shown in the table above. Of 585 patients on troglitazone, 18 patients (3.0%) had an ALT value over 3x ULN. In 9 patients (1.5%), it exceeded 8xULN. Two patients had ALT values over 30 x ULN. One of these patients developed liver failure and was given a transplant but died soon after. The second patient recovered. The median duration of troglitazone treatment to initial ALT elevation was 126 days and to peak elevation was 143 days. The highest initial ALT value for any of these patients was 0.6 x ULN.

The incidence of 3.0% for ALT > 3x ULN in the NIH trial appears higher than the 1.9% found in the NDA database. The incidence of ALT values > 30x ULN was 0.2% (5/2510) in the NDA data base and 0.3% (2/585) in the NIH study. These apparent differences may possibly be explained by the fact that about 800 patients in the NDA database had been exposed to troglitazone for less than three months and therefore were not as vulnerable to liver damage as patients who had been exposed longer. Another difference is that the ULN for ALT was adjusted for age and sex in the NIH report.

Since the first cases of liver failure which surfaced in fall 1997, DMEDP has taken the position that Prelay could be used safely provided that patients were monitored for early signs of liver damage. In July 1998, monthly monitoring was added to the label to try to prevent the rapid development of irreversible liver damage that occurred in the patient in the NIH diabetes prevention trial It has recently become apparent, however, that even monthly monitoring will not prevent every case. In January 1999**, we became aware of a 63 year old patient in a Parke-Davis postmarketing study who developed irreversible liver damage 41 days after starting Prelay. Her ALT had been normal at baseline (17) and had been normal (22) just 13 days before the ALT value of 1130. She then went on to develop liver failure and died several weeks later. That this happened in one of Parke-Davis' own studies is evidence that the safety of troglitazone cannot be assured., even with monthly monitoring of liver enzymes. (** in March 12 version this date is incorrectly given as 1998.)

In the clinical trials which led to troglitazone's approval, there were no cases of liver failure in 2510 patients (NDA data base in previous table). Now we have one death due to liver failure in a postmarketing study of about 2500. We also know of one liver transplant among the 585 patients exposed to troglitazone in the NIH diabetes prevention trial. Combining the NDA data base and the NIH trial, there were 7 patients out of 3095 (six in addition to the one liver transplant patients in the NIH trial) whose ALT value exceeded 30 x ULN, an elevation which most clinicians would consider to be dangerous. Although the numbers are too small to be confident about calculating an incidence rate, it is hard to deny that these cases create a serious doubt about the safety of troglitazone. By contrast, I am not aware of a single case of lactic acidosis, let alone a death due to lactic acidosis, in over 6,000 patients who have received metformin in clinical trials. The fact that liver failure due to troglitazone cannot always be prevented, even with monthly monitoring, requires that we redefine the patient population for which troglitazone is really needed.

*Two patients had liver biopsies showing idiosyncratic drug reaction, but only one of these patients was jaundiced. An additional patient had jaundice believed to be due to recent exposure to an environmental toxin. This error was corrected in a subsequent label.

LABELING:

Liver injury: There is now enough information about liver injury that the terms "rare" and "very rare" seem inappropriate. Classifying cases as "ALT levels greater than 3x ULN" also serves to understate the problem.

I would suggest the following language:

DRAFT LABELING

I would also expand the section about the clinical trials in the boxed warning:

DRAFT LABELING

Mechanism of action: The paragraph dealing with islet function should be omitted. Improvement in beta cell function in troglitazone-treated patients is probably a non-specific finding related to improvement in hyperglycemia.

Clinical effects: The addition of new information about lipids can be added as written, but a statement should be included indicating that the clinical significance of these lipid changes is not known.

Combination with SFU: The new paragraph dealing with body distribution should be deleted. This was from a small study with incomplete data in which troglitazone was not very effective.

Comparisons with metformin: The section " Combination with metformin" is misleading. I believe that addition of troglitazone does lead to improvement in insulin-mediated glucose disposal that cannot be achieved with metformin alone, but the data that were submitted are not convincing. In the NEJM article, one patient dropped out of troglitazone monotherapy because of lack of efficacy. Since his/her data is not included, the data given in the proposed label does not represent a true intent to treat analysis. Although metformin and troglitazone appeared to be equally effective in lowering FPG in patients who completed monotherapy, metformin appeared to lower HbA1c but not troglitazone. More than half of the troglitazone-treated patients (7/13 of the completers) failed to show a reduction of FPG of 30 mg/dl compared to 20% of metformin patients. The impressive improvement in hyperglycemia, attributed to combination therapy, during the second three-month period could arguably be a carry-over from the initial three months of monotherapy. A rigorous demonstration of the efficacy of combined therapy would have required re-randomization at the end of monotherapy with some patients continuing on monotherapy while others received combined therapy. Given this design flaw, DEMDP should reject the new indication of troglitazone combination with metformin. It should also be noted that the Sponsor has not submitted any PK data to examine possible interactions between troglitazone and metformin

Data for triple therapy, shown in the table on page 4, should divide patients according to their dose of metformin (under 2 grams vs 2 grams or more) as described earlier.

The proposed label addition regarding LDL particle size should be omitted. The study by Demacker et al (sNDA vol 11, p 319) on which the statement is based was done in non-diabetic patients. The original data from the study was not submitted for review. Similarly statements regarding PAI-1 levels (from Fonseca et al. SNDA vol 11 p 328) and B cell function (Prigeon et al sNDA vol 11 p 323) should also be deleted from the proposed label. These are small studies. The sites were never inspected and the raw data were not submitted to the division for review.

Monotherapy: Troglitazone should no longer be indicated as first-line monotherapy. The response rate, based on reduction in FPG of >30 mg/dl is only about 50%. Since liver failure related to troglitazone cannot be prevented with certainty, a risk/benefit assessment no longer justifies starting a patient on troglitazone monotherapy. On the other hand, I see no necessity to withdraw the drug from those patients who have had a good response and have been treated long enough and so that the risk of liver failure is no longer a prominent issue.

Dosage and administration: The word "adequately" should be added: [redacted] would not require that patients be treated with maximal doses of SFU or metformin before troglitazone is added. Details of the study should be included elsewhere in the label but physicians should not be constrained to use the three drugs exactly as it was in the study.

DRAFT LABELING

RECOMMENDATIONS:

Combination therapy:

Troglitazone is highly effective in patients with type 2 diabetes whose hyperglycemia is resistant to insulin treatment. These patients tend to be older than patients who do not require insulin. They are also more likely to have the kidney and heart involvement that would increase the risk of lactic acidosis if they were treated with metformin. Thus, I believe that the risk/benefit relationship for troglitazone is favorable in these patients even recognizing the possibility of liver failure. My recommendation not to restrict the use of troglitiazone in these patients stems from the belief that there is presently no alternative that offers a more favorable profile of risk and benefit. This situation may change with the development of thiazolidinediones that are more potent than troglitazone and may be less likely to injure the liver.

This submission provides strong evidence for the labeling claim that troglitazone is effective when added to patients inadequately controlled on a combination of a sulfonylurea plus metformin. These three classes of drugs work through largely different mechanisms so that triple drug combination therapy makes a good deal of sense. The label should make clear how the add-on study was done ie. order of treatment, maximal vs submaximal doses, etc but should not imply that this is necessarily the way individual patients should be treated. Since the only alternative these patients have is insulin, I believe that use of troglitazone is warranted in at least some of these patients.

Monotherapy:

Although troglitazone monotherapy is effective in some patients, it is not possible at present to select these patients except by a therapeutic trial. Because of the risk of liver failure, troglitazone should not be considered a first-line drug. Patients already on troglitazone monotherapy may be allowed to continue but new patients should not be treated. If this distinction cannot be made clear in a label, I would recommend that the monotherapy indication be withdrawn entirely. Claims of additional benefits such as improved beta cell function and decreased LDL particle size should be rejected.

Information in this submission shows that troglitazone is less reliable at controlling hyperglycemia than is metformin, and is less desirable than metformin with respect to weight reduction and lipid levels. Recent data from the UKPDS study has shown that control of hyperglycemia with metformin or sulfonylureas prevents microvascular complications of diabetes and do not increase cardiac mortality. Yet the labels for these products still contain a FDA-mandated warning about cardiovascular mortality based on the UGDP study, the results of which have largely been considered erroneous for many years. In an effort to prevent troglitazone from being used inappropriately, the UGDP warning should be removed from competing products.

/S/ [redacted]

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/DEMPD
HFD 510/misbin/sobel/malozowski
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/S/ [redacted]

8/30/99